



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/822,379	03/30/2001	Philip Stewart Low	3220-67883	5816

23643 7590 03/21/2003

BARNES & THORNBURG  
11 SOUTH MERIDIAN  
INDIANAPOLIS, IN 46204

EXAMINER
----------

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
----------	--------------

1642

DATE MAILED: 03/21/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.  
09/822,379

Applicant(s)  
Low et al

Examiner  
Karen Canella

Art Unit  
1642



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 months MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_\_.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 6-47 is/are pending in the application.
- 4a) Of the above, claim(s) 14 and 15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 6-13, and 16-47 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5,9 6) ☐ Other:

Art Unit: 1642

### DETAILED ACTION

1. Acknowledgment is made of applicants election of the species of “a compound capable of stimulating an endogenous immune response” and applicants election with traverse of Group I, drawn to a method for enhancing the endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal, wherein said population comprises cancer cells, said method comprising the administering of an immunogen conjugated to a ligand, and pharmaceutical compositions comprising ligand immunogen conjugates. The traversal is on the grounds that both groups of the restriction requirement do not adequately represent applicants claimed invention. Applicant argues that an endogenous population of pathogenic cells in a host organism can comprise an intracellular infectious agent and thus be excluded from both restriction groups. This has been carefully considered. It was the examiner intention at the time of the restriction to include endogenous pathogenic cells infected with an intracellular pathogen within Group II. Thus the restriction of the instant invention is more clearly stated by the following: Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 2, 3 and 16 and claims 1, 6-13 and 17-47, in part, drawn to a method for enhancing the endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal, wherein said population comprises cancer cells, said method comprising the administering of an immunogen conjugated to a ligand, and pharmaceutical compositions comprising ligand immunogen conjugates, classified, for example, in class 424, subclass 178.1 and class 530, subclass 391.1.
- II. Claims 4 and 5 and claims 1, 6-15 and 17-47, in part, drawn to a method for enhancing the endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal, wherein said population comprises exogenous pathogens and host cells infected by exogenous pathogens, said method comprising the administering of an immunogen conjugated to a ligand, and

Art Unit: 1642

pharmaceutical compositions comprising ligand immunogen conjugates classified in class 424, subclass 178.1 and class 530, subclass 391.1.

The inventions are distinct, each from the other because of the following reasons:

The methods of Groups I and II differ in the method objectives, method steps and parameters and in the reagents used. The ligand used for the method of Group I would not be-coextensive with the ligand used for method II because cancer cells express different receptors and proteins from cells infected by intracellular pathogens, such as M. Tuberculosis. Thus, the reagents used in the method of Group I will be structurally and functionally distinct from the reagents used in method II.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their divergent subject matter and because the searches required for the groups are not co-extensive, restriction for examination purposes as indicated is proper. It is noted that claims 14 and 15 were inadvertently placed in Group I in addition to Group II.

2. Claims 4 and 5 have been canceled. Claims 14 and 15, drawn to non-elected inventions, are withdrawn from consideration. Claims 1-3, 6-13 and 17-47 are examined on the merits.

### ***Claim Objections***

3. Claims 1, 6-26, 28-47 are objected to because of the following informalities:

(A) the claims are drawn in part to the non-elected invention of pathogenic cells comprising exogenous pathogens endogenous cells infected thereby. Appropriate correction is required.

Art Unit: 1642

(B) Claims 9 and 10 recite the word “analog”, but claims 39-42 recite “analogue”.

Applicant is advised to adopt a consistent spelling of said word. It is noted that the specification as filed uses “analog”.

4. Claim 34 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 34 is dependent on claim 31. Claim 31 is drawn to active immunization. Claim 34 specifically embodies only an innate immune response. As the active immunization results in an acquired immune response, claim 31 excludes methods specifically drawn only to an innate immune response such as claim 34.

5. Claims 8, 11 and 12 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 8 fails to further limit claim 1. Claim 1 embodies an immunogen conjugated to a ligand. Claim 8 recites the limitations of covalent, ionic or hydrogen bonding. As these limitations represent all possible mode of conjugation, and claim 1 requires “conjugation”, the limitations of claim 8 do not further limit claim 1.

Claims 11 and 12 do not further limit claims 9 and 10. Claims 9 and 10 embody a covalent linkage to the immunogen. Claims 9 and 10 specify that this linkage is by direct covalent linkage or by covalent bonding through a divalent linker, said divalent linker representing and “indirect” covalent linkage. As these limitations encompass the two possible alternatives for covalent linkage, i.e. direct or indirect, claims 11 and 12 do not further limit claims 9 and 10.

Art Unit: 1642

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 2, 3, 9-14, 17, 19, 30, 31, 35 and 43-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-12 and 39-42 recite "folic acid analog[ue]". The term "folic acid analog[ue]" is not defined by the claims, and the specification does not provide a standard in terms of structure or function for ascertaining the identity of a folic acid analog.

Claim 2 is vague and indefinite in the recitation of "tumorigenic". It is unclear if the applicant intends that "tumorigenic" refer to the transplantation of tumor cells to mice and the subsequent development versus non-development of the tumor within the mouse, or if applicant intend that tumorigenic should be limited to solid tumors rather than malignancies of the non-adherent hematopoietic cells. It noted that transplanted lymphoma cells are evaluated as to their tumorigenicity in nude mice. Further, in light of the vague and indefinite nature of claim 3 for the reasons set forth above, it is unclear how claim 3 further limits claim 2. When given the broadest reasonable interpretation both tumors and cancers are defined as malignant neoplasms.

The term "small" in claims 13 and 14 is a relative term which renders the claim indefinite. The term "small" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 17 is rendered vague and indefinite in the recitation of EphA2 as the only means for identifying the ligand binding sites. This is a laboratory designation. The use of laboratory designations only to identify a particular protein or receptor renders the claim indefinite because different laboratories may use the same laboratory designation to define completely distinct

Art Unit: 1642

proteins, or different laboratories may use different identifiers to define the same protein or receptor. Amendment of the claims to include a sequence identifier is suggested because the sequence identifier is a unique identifier which would unambiguously define a given protein or receptor.

The recitation of "organic molecule" in claims 14 and 19 lack antecedent basis in claims 12 and 17, respectively. The recitation of "non-natural process" in claims 30 and 31 lacks antecedent basis in claim 28. The recitation of "humoral response" in claims 33 and 34 lack antecedent basis in claim 31. The recitation of "acquired response" in claim 35 lacks antecedent basis in claim 32. For purpose of examination claims 14 and 19 will be considered as dependent on claims 13 and 8, respectively. Claims 30 and 31 will be considered as dependent on claim 29.

Claim 44 lacks proper antecedent basis in claim 42 as claim 44 is drawn to a product and claim 42 is drawn to a method. For purpose of examination, claim 44 will be considered as dependent on claim 43.

Claim 43 recites "a ligand immunogen conjugate capable of specific binding to a population of pathogenic cells in a host animal for the specific elimination of said cells by an acquired or innate immune response, co-administered antibodies, or directly by an immune cells in the host, a compound capable of stimulating an endogenous immune response...and a pharmaceutically acceptable carrier therefor ". It is unclear if the pharmaceutical composition requires the co-administered antibodies, the compound capable of stimulating the endogenous immune response, and the pharmaceutically acceptable carrier, or if the ligand immunogen conjugate is the only limitation of the composition. For purpose of examination, all alternatives will be considered.

Although claim 17 has antecedent basis in claim 15 for a ligand-binding site, it is noted that the ligand binding site for EphA2 is present on metastatic cancer cells, and therefore applicant may have intended claim 17 to be dependent on claim 16.

Art Unit: 1642

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 6, 8, 13, 16, 19-26 and 28-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method dependent upon molecules which bind to the folate receptor and the EphA2 receptor, does not reasonably provide enablement for vitamins that binds receptors which are not the folate receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states that “the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...”. The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring “ingenuity beyond that to be expected of one of ordinary skill in the art” (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ (CCPA 1977)). Additionally the courts have determined that “...where a statement is , on its face, contrary to generally accepted scientific principles”, a rejection for failure to teach how to make/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factor are the nature of the invention, the state of the prior art, the predictability or



Art Unit: 1642

lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

Claim 1-3, 8, 13, 16, 18-26, 28-38, 43-47 are broadly drawn to encompass any ligand binding site on a population of cancer cells. Claim 6 is specifically drawn to a method relying on a vitamin as a ligand.

The prior art teaches that substances which bind to the folic acid receptor, such as folates, may be conjugated to an immunogen and administered to a host in the presence of antibodies or T-cells which will specifically bind to said immunogen or T-cell which will specifically bind to said immunogen. The art teaches that cells which bind with the folic acid conjugate will be subjected to ADCC or complement dependent cellular toxicity or cell-mediated cytotoxicity as said conjugates will be recognized by said antibodies or effector cells. It is reasonable to conclude that this recognition takes place before said conjugates can be internalized by the target cells (see the rejections below). The art teaches that cancer cells over express the folate receptor, however, Drummond et al (Vitamins and Hormones, 2000, Vol. 60, pp. 285-332, especially page 307, under the heading "Other vitamin Receptors as Targets for Ligandoliposomes") teach that "As the receptors of these vitamins become better understood with respect to routes of internalization and expression patterns on both normal and malignant cells, further development of vitamin-targeting strategies will likely be attempted". This was published in the year 2000 and the instant application claims an effective filing date to the year 2000 as well. It is concluded that the state of the art at the time of filing was not enabling for the use of other vitamin receptors for the targets of instant ligand-immunogen conjugates because the expression patterns of these receptors were unknown and it could not be anticipated that said vitamin receptors would be up regulated on a population of cancer cells versus normal tissue to the extent that the receptor represented a differentially expressed target. Further, it was unknown how said receptors would internalize the claimed ligand-immunogen conjugates and if this would occur before ADCC or complement-

Art Unit: 1642

dependent cytotoxicity or cell-mediated cytotoxicity. Neither the art nor the disclosure provides support for the formation of conjugates between other vitamins, outside of those which bind to the folic acid receptor, wherein said conjugates will bind to a target cell which over expresses said receptor in a pathological state, and wherein said receptor will not internalize the conjugate before ADCC, complement dependent cytotoxicity or cell-mediated toxicity can occur. It is noted that “vitamins” encompass molecules which are not proteins and the specification provides no guidance to how to make these non-folate conjugates whereby the binding of a vitamin conjugate to its receptor is not impaired. The specification does not teach other vitamin receptors which would be differentially up regulated in a cancerous cell. The specification does not provide an example wherein a pathogenic cell can be targeted by means of vitamin receptors for ADCC, complement dependent cytotoxicity or cell-mediated toxicity. Given the lack of guidance in the specification and the state of the art with respect to vitamin receptors on pathogenic cells, and the unreliability in the art with respect to being able to anticipate if a conjugate will be internalized before it targets a cell for ADCC, complement dependent cytotoxicity or cell-mediated toxicity, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed invention.

10. Claims 1-6, 8-13, 16, 18-26, and 28-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 9-12 and 39-42 are reliant in part on folic acid analogs as a ligand. Claims 1-6, 8, 13, 16, 18-26, 28-38 and 43-47 also encompass in part, said folic acid analogs. A note in the rejection under 112, second paragraph above, the metes and bounds of the claims with respect to the constitution of a folic acid analog cannot be determined. The specification provides no guidance on the structural or functional attributes of a folic acid analog that would serve to

Art Unit: 1642

discern molecules which are members of this genus and molecules which are not members. The disclosure puts no limit on the amount of structural variation that can be encompassed by a folic acid analog. Further, the functional attribute of said analog has not been stated. When given the broadest reasonable interpretation "folic acid analogs" can include molecules which bind to the folate receptor as well as molecules which do not bind to the folate receptor. The disclosure of a folic-acid immunogen conjugate does not adequately describe the claimed genus because the genus is highly diverse. One of skill in the art would conclude that applicant did not disclose a representative number of species of the claimed genus. Therefore, applicant was not in possession of the claimed genus.

***Claim Rejections - 35 USC § 102***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent,; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claim 43 is rejected under 35 U.S.C. 102(b) as being anticipated by either of Frincke et al (EP 217,577) or Krantz et al (U.S. 5,547,668, reference AB of the I.D.S. submitted December

Art Unit: 1642

18, 2001) or Pouletty et al (WO 97/37690). Claim 43 is drawn to a pharmaceutical composition comprising therapeutically effective amounts of a ligand-immunogen conjugate capable of specific binding to a population of pathogenic cells in a host animal for specific elimination of said cells by an acquired or innate immune response. It is noted that the metes and bound of claim 43 cannot be determined for the reasons of record set forth in the rejection under 112, second paragraph, above.

Frincke et al disclose a pharmaceutical composition comprising a hapten-modified therapeutic agent and an anti-hapten antibody which confers upon said therapeutic agent an extended serum half-life and permits increased concentration at in vivo target sites (page 4, lines 1-3, 25-32). Frincke et al specifically disclose methotrexate as a therapeutic agent. Methotrexate binds to the folate receptor which is up regulated in tumor cells. Frincke et al also disclose Doxorubicin which has shown to selectively accumulate in certain types of human and murine tumors (page 7, lines 54-57). Thus Frincke et al disclose a pharmaceutical composition comprising a therapeutically effective amount of a ligand-immunogen conjugate capable of specific binding to a population of pathogenic cells in a host animal. It would be inherent in the prior art ligand hapten conjugates and anti-hapten antibodies that the cells to which the composition binds would be eliminated by the innate immune response through ADCC or complement mediated cytotoxicity. Thus the disclosure of Frincke et al meets the limitations of claim 43 in light of the rejection under 112, second paragraph.

Kranz et al disclose a composition comprising an anti-T-cell receptor antibody conjugated to folate, wherein the innate immune response, i.e., the activated T-cell, eliminates the targeted folate receptor cells (column 2, lines 8-40). Thus the disclosure of Kranz et al meets the limitations of claim 43 in light of the rejection under 112, second paragraph.

Pouletty et al disclose a composition comprising a moiety capable of specifically binding to a target cell joined to a selective moiety for binding to an endogenous effector agent capable of causing cytotoxicity to destroy cell associated with a pathogenic condition (abstract). Pouletty et

Art Unit: 1642

al diclose folate as a moiety which is capable of binding to high affinity receptors on many tumor cells (page 5, lines 3-9) and the alpha-galactosyl epitope as the selective moiety, wherein the host has natural antibodies or to which the host has been previously sensitized (page 6, lines 10-32 and page 7, lines 13-19).

13. Claim 43 is rejected under 35 U.S.C. 102(e) as being anticipated by Cowan (WO 01/32207). Cowan discloses a pharmaceutical composition comprising a hapten or immunogen, wherein said hapten or immunogen is conjugated to an antigen binding ligand. (abstract). Cowan discloses that the elimination of said targeted cell is by means of an acquired immune response (page 6, second paragraph to page 7, line 2).

14. Claims 1-8, 13, 26, 36, 43 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Roy et al (International Journal of Cancer, 1998, Vol. 76, pp. 761-766, reference AZ of the I.D.S. submitted December 18, 2001). The specific limitations of claim 43 are recited above. Claim 1 embodies method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein the members of said cell population have an accessible binding site for a ligand, said method comprising the step of administering to said host a composition comprising an immunogen conjugated to a ligand, wherein said immunogen is known to be recognized by an endogenous or an exogenous antibody in the host or is known to be recognized directly by an immune cell in the host; and administering to said host a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate. Claim 2 embodies the method of claim wherein the population of pathogenic cells is a cancer cell population. Claim 3 embodies the method of claim 2 wherein the cancer cell population is tumorigenic. Claim 6 embodies the method of claim 1 wherein the ligand is a vitamin capable of specifically binding to a cell membrane receptor. Claim 7 embodies the method of claim 6

Art Unit: 1642

wherein the ligand is selected from the group consisting of folic acid and other folate receptor-binding ligand. Claim 8 embodies the method of claim 1 wherein the ligand is chemically complexed to the immunogen through bonding comprising covalent, ionic, or hydrogen bonding. Claim 13 embodies the method of claim 1 wherein the ligand is a small organic molecule capable of binding to a receptor and wherein said receptor is preferentially expressed, uniquely expressed or over expressed on the surface of said population of pathogenic cells. Claim 26 embodies the method of claim 21 wherein the therapeutic factor comprises at least one NK cell or T cell stimulant. Claim 36 embodies the method of claim 1 wherein the endogenous immune response comprises a cell-mediated immune response. Claim 47 is drawn to method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein the members of said cell population have an accessible binding site for a ligand, said method comprising the step of administering to said host a ligand-immunogen conjugate composition comprising a complex of the ligand and an immunogen wherein said immunogen is known to be recognized by an endogenous or an exogenous antibody in the host or is known to be recognized directly by an immune cell in the host; and administering to said host a therapeutic factor, said factor being selected from the group consisting of a cell killing agent, a tumor penetration enhancer, a chemotherapeutic agent, an antimicrobial agent, a cytotoxic immune cell, and a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate.

Roy et al disclose a method of enhancing an endogenous immune response comprising the administration of SEB which is a T-cell stimulant and a folate attached directly to an anti-T-cell receptor antibody for the elimination of tumor cells by a cell-mediated immune response, wherein the immunogen is the anti-T-cell antibody recognized by T-cells in the host.

Art Unit: 1642

***Claim Rejections - 35 USC § 103***

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

16. (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frincke et al (EP 217,577) in view of any of Cady et al (U.S. 5,266,333) or Schroder (U.S. 4,713,249) or Modi (U.S. 5,417,982). Claim 44 embodies the pharmaceutical composition of claim 43, wherein the composition is in a parenteral prolonged release dosage form. Frincke et al teach the specific embodiments of claim 43 for the reasons set forth above. Frincke et al teach the desirability of prolonging the period of administration to maintain an effective concentration of a therapeutic agent sufficient to achieve desired results. Frincke et al do not teach the pharmaceutical composition in parenteral prolonged release dosage form. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to put the pharmaceutical composition of Frincke et al into parenteral prolonged release dosage form.

Art Unit: 1642

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of any of Cady et al or Schroder or Modi on the means for formulating therapeutic agents in parenteral prolonged release dosage form and the teachings of Frincke et al teach the desirability of prolonging the period of administration of a therapeutic agent.

18. Claims 1-3, 8, 18, 19, 22, 29, 31-33, 35-37, 43 and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cowan (WO 01/32207) in view of Smith (WO 97/41831) and Insel (Annals of the New York Academy of Science, 1995, Vol. 754, pp. 35-47). The specific limitations of claims 1-3, 8, 26, 36 and 47 are set forth above.

Claim 18 embodies the method of claim 1 wherein the immunogen is an organic molecule having a molecular weight less than 20,000 Daltons. Claim 19 embodies the method of claim 17 wherein the organic molecule is fluorescein or dinitrophenyl. Claim 22 embodies the method of claim 1 wherein the therapeutic factor comprises a cytokine. Claim 23 embodies the method of claim 21 wherein the therapeutic factor comprises IL-2, IL-12, IL-15, or combinations thereof. Claim 24 embodies the method of claim 21 wherein the therapeutic factor comprises IL-2, IL-12, IL-15, or combinations thereof, in combination with IFN-.alpha or IFN-.gamma. Claim 25 embodies the method of claim 21 wherein the therapeutic factor comprises IL-2, IL-12, IL-15, or combinations thereof, in combination with IFN-.alpha. or IFN-.gamma., or a combination thereof, and GM-CSF. Claim 29 embodies the method of claim 1 wherein the host animal had been previously exposed to the immunogen by a non-natural process resulting in priming of the host animal's immune response to said immunogen. Claim 31 embodies the method of claim 29 wherein the non-natural process resulting in priming of the immune response is vaccination. Claim 32 embodies the method of claim 1 wherein the endogenous immune response comprises a humoral immune response. Claim 33 embodies the method of claim 31 wherein the humoral response is an acquired immune response. Claim 35 embodies the method of claim 32 wherein the



Art Unit: 1642

acquired response is induced by administering into the host animal a vaccine composition. Claim 37 embodies the method of claim 1 wherein the endogenous immune response comprises a humoral and a cell-mediated immune response. Claim 45 embodies the pharmaceutical composition of claim 42 wherein the therapeutic factor is an immune stimulant. Claim 46 embodies the pharmaceutical composition of claim 44 wherein the immune stimulant comprises a compound selected from the group consisting of IL-2, IL-12, IL-15, IFN-.alpha., IFN-.gamma., and GM-CSF, or combinations thereof.

Cowan et al teach a method for of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein the members of said cell population have an accessible binding site for a ligand, said method comprising the step of administering to said host a a composition comprising an immunogen conjugated to a ligand, wherein said immunogen is known to be recognized by an endogenous or an exogenous antibody in the host or is known to be recognized directly by an immune cell in the host. Cowan teaches that immunogens can be selected such that a humoral, cellular or humoral and cellular response to the target antigen is selected (page 9, first paragraph and page 11, under the heading "Example 4") an that DNP can stimulate humoral immunity to DNP. Cowan et al teach that the target antigen can be on a cancer cell (page 8, line 3). Cowan et al teach the administration of an immunogen, or a hapten-immunogen conjugate for a sufficient amount of time in order to confer on the patient humoral immunity to the hapten and cellular immunity to the immunogen (page 8, first full paragraph), thus teaching the specific embodiments of claims 1-3, 8, 18, 19, 29, 31-33, 35-37, 43, and 45-47 with the exception of the administration of a compound capable of stimulating an endogenous immune response. Cowan et al teach the proliferation of activated immune cells having binding sites for the immunogen (page 8, first full paragraph). Cowan does not teach the administering to said host a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate.

Art Unit: 1642

Smith teaches the stimulation of the immune response in human by the administration of Il-2, Il-12, Il-15, INF-alpha and INF-gamma (page 10). Smith et al suggest the use of these cytokines along with folic acid analogues (page 26, lines 31-32).

Insel teach that Il-2 and INF-gamma and TNF-beta activates macrophage to mediate the delayed hypersensitivity and that Il-4, Il-5, Il-6 and Il-10 provide help to B-cells for antibody production.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer cytokines to activate macrophages for the Th1 response and administer cytokines to provide B-cell help. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Cowan on the desirability of eliciting both humoral and cell-mediated immunity and the teachings of Insel on the specific cytokines associated with cell mediated immunity (Th1) and humoral immunity (Th2), and the teachings of Smith et al on the stimulation of the human immune system by the administration of cytokines.

19. Claims 1-3, 6-8, 11, 13, 18-26, 28-35, 38, 39, 43, 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty (WO 97/37690) in view of Smith (WO 97/41831) and Insel (Annals of the New York Academy of Science, 1995, Vol. 754, pp. 35-47) and the abstract of Mazzoni et al (Proc Annu Meet Am Assoc cancer Res, 1997, Vol. 38, page A558). The specific limitations of claims 1-3, 6-8, 13, 18, 19, 22-26, 29-33, 35, 43, 45-47 are set forth above.

Claim 20 embodies the method of claim 1 wherein the immunogen is an .alpha.-galactosyl group. Claim 21 embodies the method of claim 1 wherein the antibody is exogenous to said host and is co-administered with said conjugate composition. Claim 28 embodies the method of claim 1 wherein the host animal had been previously exposed naturally to the immunogen so that the host animal has a preexisting immunity to said immunogen evidenced by the presence of endogenous antibodies to the immunogen. Claim 30 embodies the method of claim 28 wherein

Art Unit: 1642

the non-natural process resulting in priming of the animal's immune response is vaccination. Claim 31 embodies the method of claim 28 wherein the non-natural process resulting in priming of the immune response is active immunization. Claim 34 is drawn to an innate humoral immune response. Claim 38 embodies a method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein said population expresses a binding site for a ligand, said method comprising the steps of administering to the host a composition comprising a complex of said ligand and an immunogen; administering to the host antibodies directed against the immunogen; and administering to said host a compound which stimulates an endogenous immune response that does not bind to the ligand-immunogen complex.

Pouletty et al teach a method for enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein the members of said cell population have an accessible binding site for a ligand, said method comprising the step of administering to said host a composition comprising an immunogen conjugated to a ligand, wherein said immunogen is known to be recognized by an endogenous or an exogenous antibody in the host or is known to be recognized directly by an immune cell in the host. Pouletty et al teach alpha-galactosyl as an immunogen, wherein the host has natural antibodies or to which the host has been previously sensitized (page 6, lines 10-32 and page 7, lines 13-19) either through natural exposure or previous vaccination. Pouletty et al teach folate as a ligand which is capable of binding to high affinity receptors on many tumor cells (page 5, lines 3-9). Pouletty et al teach immunogens as including antigens to which the host has been previously sensitized due to a prior immune response, such as diphtheria, tetanus, influenza, polio, rubella or measles (page 6, lines 16-22). Pouletty et al teach that the anti-immunogen antibodies may interact with members of the complement cascade or induce ADCC to kill the target cell, or the immunogen may bind to a T-cell that provides a cytotoxic function (page 6, lines 30-32). Pouletty et al teach folate as a binding moiety for tumor cells (page 5, lines 3-9),

Art Unit: 1642

the immunogen of fluorescein (page 15, paragraphs 2 and 3) and the administration of exogenous anti-FITC antibodies (page 18, lines 28-30). Thus, Pouletty teach all the embodiments of the claims 1-3, 6-8, 11, 13, 18-26, 28-35, 38, 39, 41, 43, 45-47 with the exception of the administration of the compound capable of stimulating an endogenous immune response.

Smith teaches the stimulation of the immune response in human by the administration of IL-2, IL-12, IL-15, INF-alpha and INF-gamma (page 10). Smith et al suggest the use of these cytokines along with folic acid analogues (page 26, lines 31-32).

Insel teach that IL-2 and INF-gamma and TNF-beta activates macrophage to mediate the delayed hypersensitivity and that IL-4, IL-5, IL-6 and IL-10 provide help to B-cells for antibody production.

The abstract of Mazzoni et al (Proc Annu Meet Am Assoc cancer Res, 1997, Vol. 38, page A558) teaches that IL-2 is important to support the growth of effector cells in immunotherapy of cancer.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer cytokines to activate macrophages for the Th1 response and administer cytokines to for the Th2 response to provide B-cell help. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Mazzoni et al on the importance of IL-2 in maintaining effector cells during immunotherapy of cancer, the teachings of Insel on the importance of specific cytokines on the proliferation of T and B cells and the teachings of Smith et al on the administration of cytokines to humans as adjuvants

20. Claims 39 and 40 rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty (WO 97/37690) in view of the abstract of Leamon et al (Journal of Drug Targeting, 1999, Vol. 7, pp. 157-169). Claim 39 is drawn to a method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal

Art Unit: 1642

harboring said population wherein said population preferentially expresses, uniquely expresses, or over expresses a folic acid receptor, said method comprising the step of administering to said host a composition comprising a covalently linked conjugate of an immunogen wherein the immunogen is known to be recognized by an endogenous or exogenous antibody in the host or is known to be recognized directly by an immune cell in the host; and a ligand comprising folic acid or a folic acid analogue having a glutamyl group wherein the covalent linkage to the immunogen is only through the .gamma.-carboxyl group of the glutamyl group. Claim 40 is drawn to a method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein said population preferentially expresses, uniquely expresses, or over expresses a binding site for a folic acid receptor, said method comprising the step of administering to said host a composition comprising a covalently linked conjugate of an immunogen wherein the immunogen is known to be recognized by an endogenous or exogenous antibody in the host or is known to be recognized directly by an immune cell in the host; and a ligand comprising folic acid or a folic acid analogue having a glutamyl group wherein the covalent linkage to the immunogen is only through the alpha carboxyl group of the glutamyl group.

Pouletty et al teach a method for enhancing the endogenous immune response comprising the administration of a covalently linked conjugate of a folate to an immunogen, wherein the conjugation of folic acid to immunogens through carboxyl groups. Pouletty et al do not specifically teach the alpha glutamyl carboxyl group or the gamma glutamyl carboxyl group.

The abstract of Leamon et al teaches that although folic acid coupled to peptides by either an alpha or glutamyl linkage associates with folic acid receptor bearing cells at identical levels to non-conjugates folic acid.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to conjugate folic acid to the immunogen through either the alpha or gamma glutamyl groups. One of ordinary skill in the art would have been motivated to do so with

Art Unit: 1642

a reasonable expectation of success by the teachings of the abstract of Leamon et al on the equivalent association of alpha or gamma coupled folic acid to the folic acid receptor.

21. Claims 1-3, 6-13, 18-26, 28-35, 38-43 and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty (WO 97/37690) in view of the abstract of Leamon et al (Journal of Drug Targeting, 1999, Vol. 7, pp. 157-169) as applied to claims 39 and 40 in section 21 above, and further in view of Smith (WO 97/41831) and Insel (Annals of the New York Academy of Science, 1995, Vol. 754, pp. 35-47) and the abstract of Mazzoni et al (Proc Annu Meet Am Assoc cancer Res, 1997, Vol. 38, page A558). Claim 9 embodies the method of claim 8 wherein the ligand is a folic acid analog having a glutamyl moiety covalently linked to the immunogen only via the glutamyl .gamma.-carboxyl moiety of the ligand. Claim 10 embodies the method of claim 8 wherein the ligand is a folic acid analog having a glutamyl moiety covalently linked to the immunogen only via the glutamyl .alpha.-carboxyl moiety of the ligand. Claim 11 embodies the method of claim 9 wherein the covalent linkage between the immunogen and the ligand is by direct covalent bonding to the immunogen or by covalent bonding through a divalent linker. Claim 12 embodies the method of claim 10 wherein the covalent linkage between the immunogen and the ligand is by direct covalent bonding to the immunogen or by covalent bonding through a divalent linker. It is noted that claim 12 encompasses all possible alternatives for the conjugation of the immunogen and the ligand and thus fails to further define claim 10. Claim 41 is drawn to a method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein said population preferentially expresses, uniquely expresses, or over expresses a binding site for a folic acid receptor, said method comprising the steps of administering to said host a composition comprising a covalently linked conjugate of an immunogen wherein the immunogen is known to be recognized by an endogenous or exogenous antibody in the host or is known to be recognized directly by an immune cell in the host; a ligand comprising folic acid or a folic acid analogue

Art Unit: 1642

having a glutamyl group wherein the covalent linkage is only through the .gamma.-carboxyl group of the glutamyl group; and administering to the host a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate. Claim 42 is drawn to a method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein said population preferentially expresses, uniquely expresses, or over expresses a folic acid receptor, said method comprising the step of administering to said host a composition comprising a covalently linked conjugate of an immunogen wherein the immunogen is known to be recognized by an endogenous or exogenous antibody in the host or is known to be recognized directly by an immune cell in the host; a ligand comprising folic acid or a folic acid analogue having a glutamyl group wherein the covalent linkage is only through the alpha.-carboxyl group of the glutamyl group; and administering to the host a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate.

The combination of Pouletty et al and the abstract of Leamon et al renders obvious claims 39 and 40 fro the reasons set forth above. Pouletty et al teaches the specific embodiments of the claim 1-3, 6-13, 18-26, 28-35, 38, 41-43 and 45-47 with the exception of the administration of a compound capable of stimulating an endogenous immun response.

Smith teaches the stimulation of the immune response in human by the admiinistration of Il-2, Il-12, Il-15, INF-alpha and INF-gamma (page 10). Smith et al suggest the use of these cytokines along with folic acid analogues (page 26, lines 31-32).

Insel teach that Il-2 and INF-gamma and TNF-beta activates macrophage to mediate the delayed hypersensitivity and that Il-4, Il-5, Il-6 and Il-10 provide help to B-cells for antibody production.

Art Unit: 1642

The abstract of Mazzoni et al (Proc Annu Meet Am Assoc cancer Res, 1997, Vol. 38, page A558) teaches that Il-2 is important to support the growth of effector cells in immunotherapy of cancer.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer cytokines to activate macrophages for the Th1 response and administer cytokines to for the Th2 response to provide B-cell help. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Mazzoni et al on the importance of Il-2 in maintaining effector cells during immunotherapy of cancer, the teachings of Insel on the importance of specific cytokines on the proliferation of T and B cells and the teachings of Smith et al on the administration of cytokines to humans for adjuvants.

22. Claims 1-3, 6-9, 11, 13, 16-35, 38, 39, 41-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty (WO 97/37690) in view of Smith (WO 97/41831) and Insel (Annals of the New York Academy of Science, 1995, Vol. 754, pp. 35-47) and the abstract of Mazzoni et al (Proc Annu Meet Am Assoc cancer Res, 1997, Vol. 38, page A558) as applied to claims 1-3, 6-9, 11, 13, 16-26, 28-35, 38, 39, 41-43, 45-47 above and further in view of any of Cady et al (U.S. 5,266,333) or Schroder (U.S. 4,713,249) or Modi (U.S. 5,417,982) above

The specific embodiments of claims 1-3, 6-9, 11, 13, 16-26, 28-35, 38, 39, 41-47 are set forth above. Claim 27 embodies the method of claim 1 wherein the ligand-immunogen conjugate composition is administered in multiple injections. Pouletty et al do not teach the pharmaceutical composition in parenteral prolonged release dosage form or the administration of multiple injections of the ligand immunogen composition. Cady et al (U.S. 5,266,333) or Schroder (U.S. 4,713,249) or Modi teach parenteral prolonged release dosage forms. Modi et al also teach that many drugs are susceptible to degradation at the site of injection and consequently require multiple injections in order to achieve the desired efficacy. Modi et al further teach that the



Art Unit: 1642

controlled release formulation of the drug can provide a delivery system that is more cost efficient than previous delivery systems (column 1, lines 12-21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to put the pharmaceutical composition rendered obvious by Pouletty and Smith and Insel and the abstract of Mazzoni et al into a prolonged release form or to administer the aforesaid composition in multiple injections. One of ordinary skill in the art would have been motivated to do by the teachings of Modi et al on the need to administer multiple injections or prolonged release form of a drug in order to achieve desirable therapeutic benefit.

23. Claims 1-3, 8, 16-19, 22, 29, 31-33, 35-37, 43 and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cowan (WO 01/32207) in view of Smith (WO 97/41831) and Insel (Annals of the New York Academy of Science, 1995, Vol. 754, pp. 35-47) as applied to claims 1-3, 8, 18, 19, 22, 29, 31-33, 35-37, 43 and 45-47 in section 18 above, and further in view of the abstracts of Easty et al (International journal of Cancer, 1999, Vol. 84, pp 494-501) and Walker-Daniels et al (Prostate, 1999, vol. 41, pp. 275-280). The combination of Cowan and Insel and Smith renders obvious the embodiments of claims 1-3, 8, 18, 19, 21-26, 29, 32, 33, 35-37, 43 and 45-47 for the reason set forth above.

Claim 16 embodies the method of claim 1 wherein the ligand binding site is an antigen preferentially expressed, uniquely expressed or over expressed on metastatic cancer cells. Claim 17 embodies the method of claim 15 wherein the ligand binding site is EphA2.

Cowan teaches ligand binding sites on cancer cells (page 7, bridging paragraph). Cowan does not teach antigens which are ligand binding sites, wherein said ligand binding sites are over expressed or uniquely expressed on metastatic cancer cells, nor does Cowan does not teach the ligand binding site of EphA2.

The abstracts of Easty and Walker-Daniels teach the up regulation of the EphA2 antigen on metastatic melanomas and metastatic prostate cells.

Art Unit: 1642

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the specific EphA2 antigen for the tumor antigen in the method rendered obvious by the combination of Cowan and Insel and Smith. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstracts of Easty et al and Walker-Daniels on the differential expression of the EphA2 antigen on metastatic melanoma and prostate cells versus cell in the primary tumor. One of skill in the art would be motivated to target the ligand immunogen conjugate to metastatic cells in order to stop the spread of cancer in a patient.

24. Claims 1-3, 6-8, 11, 13, 16-26, 28-35, 38, 39, 43 and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty (WO 97/37690) in view of Smith (WO 97/41831) and Insel (Annals of the New York Academy of Science, 1995, Vol. 754, pp. 35-47) and the abstract of Mazzoni et al (Proc Annu Meet Am Assoc cancer Res, 1997, Vol. 38, page A558) as applied to claims 1-3, 6-8, 11, 13, 18-26, 28-35, 38, 39, 43, and 45-47 in section 19 above and further in view of the abstracts of Easty et al (International journal of Cancer, 1999, Vol. 84, pp 494-501) and Walker-Daniels et al (Prostate, 1999, vol. 41, pp. 275-280). The specific embodiments of the claims are set forth above. The combination of Pouletty and Smith and Insel and the abstracts of Mazzoni and Easty and Walker-Daniels renders obvious the instant claims for the reason set forth above. Pouletty et al do not teach the EphA2 antigen as a ligand binding site.

The abstracts of Easty and Walker-Daniels teach the up regulation of the EphA2 antigen on metastatic melanomas and metastatic prostate cells.

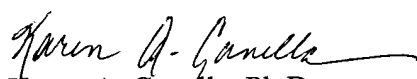
It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the specific EphA2 antigen for the tumor antigen in the method rendered obvious by the combination of Pouletty et al and Smith and Insel and the abstract of Mazzoni.

Art Unit: 1642

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstracts of Easty et al and Walker-Daniels on the differential expression of the EphA2 antigen on metastatic melanoma and prostate cells versus cell in the primary tumor. One of skill in the art would be motivated to target the ligand immunogen conjugate to metastatic cells in order to stop the spread of cancer in a patient.

***Conclusion***

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

  
Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

March 10, 2003